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How can this be? Preventing death in patients with HIV-associated tuberculosis

Barbara J. Marston and **Kevin M. De Cock**

Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Kevin M. De Cock: kmd2@cdc.gov

In 2010, some 350 000 deaths occurred worldwide among the 1 100 000 persons afflicted with both tuberculosis (TB) and human immunodeficiency virus (HIV) infection,[1] despite the fact that we have effective treatments for both. How can this be? It was recognized early on in the AIDS (acquired immunedeficiency syndrome) pandemic that outcomes of TB treatment were substantially worse for people infected with HIV, and that those who were most immunosuppressed had the worst prognosis.[2] The past few years have seen a steady surge of new information, which should reduce this inequity, regarding more effective diagnostic tools and optimal use of antiretroviral therapy (ART). Achieving public health impact, however, is more difficult, and in this issue of the *Journal*, Kumar and others examine the 15% mortality rate among persons with co-infection under India's TB control program.[3]

What are the options for preventing death among persons with co-infection? Much can be done before the onset of disease—both early ART and provision of isoniazid preventive therapy (IPT) to persons with HIV reduce the risk of developing active TB. Once a diagnosis of HIV-associated TB is made, three key interventions are available: treatment for TB (with any needed modifications of treatment regimens specific for those with co-infection), treatment for additional co-morbidities, and treatment for HIV. As high mortality in co-infected patients is driven by advancing immunodeficiency, ART has to be considered a critical part of the response. And because ART is the only intervention that directly affects underlying pathogenesis by restoring immune function, other interventions have to be re-examined in the context of provision of ART.

There is reason for concern about the specific approach to TB treatment in co-infected individuals. In 2010 Khan et al. reviewed the results from 27 studies of TB treatment outcome in the setting of HIV, and advised consideration of longer duration of therapy and daily rather than intermittent initial dosing.[4] Unfortunately, most of the data were from observational studies rather than clinical trials, it was generally not possible to distinguish relapse from re-infection and, most importantly, few of the patients driving the analysis of duration and frequency of dosing had access to ART. Conclusions about outcomes in relation to different anti-tuberculosis treatment regimens in co-infected patients in the pre-ART era may be moot in the presence of ART, and questions about optimal duration and

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dosing of TB treatment may need to be addressed anew. Prophylaxis with cotrimoxazole is a critical intervention in settings where ART cannot be accessed, and is advised under World Health Organization guidelines for all co-infected persons,[5] but its effects also may be overshadowed by ART.

That ART was an essential intervention for patients with HIV disease was never in question, but concerns about co-toxicities, adherence, and risks associated with immune reconstitution inflammatory syndrome (IRIS) caused reservations about the optimal timing of ART for patients with HIV-associated TB. Recent trials have contributed definitive insights in this regard. The Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial first reported on a broad question: for patients with HIV and confirmed pulmonary TB, was it better to begin ART during TB treatment ('integrated therapy') or to wait until TB treatment had been completed?[6] Across a range of CD4 cell counts, integrated therapy was shown to be superior; the sequential treatment arm was discontinued by the safety monitoring committee based on a 56% lower risk of death in the integrated arm.[6]

More detailed information about when best to start ART comes from analyses of the remaining arms in SAPIT[7] and three other recently reported trials—the Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA) study,[8] the AIDS Clinical Trials Group Study A5221,[9] and a study of the timing of ART in HIV-associated tuberculous meningitis.[10] Interpretation of the results requires attention to the characteristics of enrolled patients and subgroup analyses; the optimal approach may differ depending on the degree of immune suppression, the site of TB disease, and the certainty of the TB diagnosis. Regardless of the differences in the trials, the broad conclusions are that immediate initiation of ART is indicated for patients with HIV-associated pulmonary TB and CD4 counts <50 cells/μl; that for those with known higher CD4 counts a delay until 8 weeks post-diagnosis may be safe and should result in fewer complications; and that for patients with HIV-associated TB meningitis, rates of both complications of ART and mortality remain high and mortality reduction will likely depend on additional interventions, but especially on earlier diagnosis. From a practical and programmatic perspective, the best approach may be to initiate therapy early (within 4 weeks) for all HIV patients with active TB. While there may be some cost in terms of rates of IRIS, this could avoid dangerous delays—for example while seeking CD4 cell counts where these are not easily available.

The report from India's national TB program identifies access to ART as a priority for HIV-infected TB patients. We agree with this assessment: for HIV-infected patients with TB, the advent of ART has been as significant an advance as the introduction of anti-tuberculosis therapy itself.[11] There is no excuse for national TB programs not to strive for universal HIV testing of TB patients and implement early ART through a public health approach. For clinicians treating individual patients, the subtleties of how to introduce ART immediately for TB patients with advanced immunosuppression have been greatly clarified. Although research questions remain, broad conclusions continue to solidify: we need increased HIV testing, application of the '3 Is' (IPT, intensified case finding, infection control), and increased and earlier access to ART for all those living with HIV so that TB can be prevented in the first place and treated better if it does occur. Death from TB in persons living with HIV need not be.

References

1. World Health Organization. Global tuberculosis control 2011. WHO/HTM/TB/2011.16. Geneva, Switzerland: WHO; 2011. http://www.who.int/tb/publications/global_report/en/ Accessed March 2012
2. Ackah AN, Coulibaly D, Digbeu H, et al. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Côte d'Ivoire. Lancet. 1995; 345:607–610. [PubMed: 7898177]
3. Kumar A, Kumar AMV, Gupta D, Kanchar A, et al. Global guidelines for treatment of tuberculosis among persons living with HIV: un resolved issues. Int J Tuberc Lung Dis. 2012; 16:573–578. [PubMed: 22507931]
4. Khan FA, Minion J, Pai M, et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. Clin Infect Dis. 2010; 9:1288–1299. [PubMed: 20353364]
5. World Health Organization. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. Geneva, Switzerland: WHO; 2006. http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf Accessed March 2012
6. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med. 2010; 362:697–706. [PubMed: 20181971]
7. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med. 2011; 365:1492–1501. [PubMed: 22010915]
8. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med. 2011; 365:1471–1481. [PubMed: 22010913]
9. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med. 2011; 365:1482–1491. [PubMed: 22010914]
10. Török ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV) associated tuberculous meningitis. Clin Infect Dis. 2011; 52:1374–1383. [PubMed: 21596680]
11. Corbett EL, Marston B, Churchyard GJ, De Cock KM. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. Lancet. 2006; 367:926–937. [PubMed: 16546541]